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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/580,523	05/30/2000	Xiao-Mai Zhou	A7483	8284

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/580,523	Applicant(s) ZHOU, XIAO-MAI	
	Examin r MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,10,13,16,19,25,28 and 31-62* is/are pending in the application.

4a) Of the above claim(s) *31-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,10,13,16,19,25 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened to include rejection not previously cited.

It is noted that applicant has paid for a Notice of Appeal. Applicant can either request a refund or place the funds on credit for future appeals.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1-3, 10, 13, 16, 19, 22, 25 and 28 are being examined.

The following are the remaining rejections.

CLAIM CANCELLATION

Applicant request of not canceling claims that are drawn to methods of making and using the mutant BAD protein is acknowledged.

The cancellation of these claims is delayed until the time of allowance, if the claims are allowable.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH, NEW REJECTION

Claims 13, 25, 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 13 is indefinite, because claim 13 recites the limitation " said domain " . There is insufficient antecedent basis for this limitation in the claims 1 and 10, to which claim 13 is dependent.

2. Claim 25 is indefinite, because claim 25 is confusing. Claim 25 is drawn to a polypeptide or fragment thereof of claim 1, comprising the amino acid sequence corresponding to positions 103-123 of SEQ ID NO:1. It is noted that the amino acid sequence corresponding to positions 103-123 of SEQ ID NO:1 is a fragment of the wild type human BAD, having Serine at position 118 (see Sequence listing, SEQ ID NO:1). Claim 25 however is dependent on claim 1, which is drawn to a mutated BAD which does not have Serine at a position corresponding to position 118 of SEQ ID NO:1.

3. Claim 28 is indefinite because claim 28 recites the limitation "said naturally-occurring or wild-type mammalian BAD" . There is insufficient antecedent basis for this limitation in claim 1, to which claim 28 is dependent.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

1. Claims 1-3, 10, 13, 19, 22, 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide or fragment thereof, wherein a) said polypeptide or fragment thereof is at least 95% homologous to SEQ ID NO:1, b) said polypeptide or fragment thereof has Alanine at a position corresponding to the position 118 of SEQ ID NO:1, said position being identified by alignment of the amino acid sequence of said polypeptide or fragment thereof to the BH3 domain of SEQ ID NO:1, and c) said polypeptide or fragment thereof has cell death promoting activity *in*

vitro, does not reasonably provide enablement for a polypeptide or fragment thereof, wherein a) said polypeptide or fragment thereof is at least 95% homologous to SEQ ID NO:1, b) said polypeptide or fragment thereof "does not have a Serine" at a position corresponding to the position 118 of SEQ ID NO:1, said position being identified by aligment of the amino acid sequence of said polypeptide or fragment thereof to the BH3 domain of SEQ ID NO:1, and c) said polypeptide or fragment thereof has cell death promoting activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-3, 10, 13, 19, 22, 28 are drawn to a polypeptide or fragment thereof, comprising a mutant Bcl-X_L /Bcl-2 associated cell death regulator (BAD), wherein a) said polypeptide or fragment thereof is at least 95% homologous to SEQ ID NO:1, or identical to SEQ ID NO:1, except that the amino acid at position corresponding to position 118 of SEQ ID NO:1 is "an amino acid other than Serine", b) said polypeptide or fragment thereof "does not have a Serine" at a position corresponding to the position 118 of SEQ ID NO:1, said position being identified by aligment of the amino acid sequence of said polypeptide or fragment thereof to the BH3 domain of SEQ ID NO:1, and c) said polypeptide or fragment thereof has cell death promoting activity. The amino acid at said position corresponding to position 118 of SEQ ID NO:1 is not Glycine, or Alanine.

Claims 1-3, 10, 13, 19, 22, 28 encompass a polypeptide or fragment thereof, comprising a mutant Bcl-X_L /Bcl-2 associated cell death regulator (BAD), wherein a) said

polypeptide or fragment thereof is at least 95% homologous to SEQ ID NO:1, or identical to SEQ ID NO:1, except that the amino acid at position corresponding to position 118 of SEQ ID NO:1 is "any amino acid other than Serine", b) said polypeptide or fragment thereof has "any amino acid other than Serine" at a position corresponding to the position 118 of SEQ ID NO:1, said position being identified by aligment of the amino acid sequence of said polypeptide or fragment thereof to the BH3 domain of SEQ ID NO:1, and c) said polypeptide or fragment thereof has cell death promoting activity. The amino acid at said position corresponding to position 118 of SEQ ID NO:1 is not glycine, or alanine.

The specification discloses a mutation of murine BAD of SEQ.ID NO:2, wherein the serine at position 155 is replaced by Alanine, abolishes the phosphorylation of the murine BAD, and heterodimer formation with Bcl-X_L , and wherein Serine 155 is located at the center of the BH3 domain, and phosphorylation of Serine 155 promotes cell survival (Examples 1-2, on pages 72-77, and Example 9 on pages 87-93). The specification also discloses that BAD is a death promoter polypeptide, when heterodimerization with Bcl-X_L, a survival promoter, suppresses the survival promoting activity of Bcl-X_L, and promotes cell death activity. The specification discloses that phosphorylation of BAD at Serine 112, or Serine 136 or Serine 155 of murine BAD of SEQ ID NO:2 would abolish the binding of BAD to Bcl-2 or Bcl-X_L , and thus abolish the death promoting activity of BAD (p.4, first paragraph and Examples 1-2, 9). The specificataion discloses that SEQ ID NO:1 is the human BAD, wherein the serine at position 118 correspond to the serine 155 of the murine BAD of SEQ ID NO:2 (p.7, and

40-41, and table 1 on page 42). The specification further discloses mutants of BAD having a domain substantially similar to the BH3 domain, and an amino acid different from Serine at a position corresponding to position 118 of SEQ ID NO:1, as identified by alignment of the mutant sequences with SEQ ID NO:1 (p. 10-17). There is however no disclosure that these mutants have cell death promoting activity.

The specification further discloses that when Serine 155 of murine BAD is replaced with Aspartic acid (S155D), there is no pro-apoptotic activity of the S155D mutated BAD as compared to wild type BAD (p.89, second paragraph, and figure 12C).

It is noted that it is well known in the art that substitution of Serine with Alanine is a conservative substitution.

It is further noted that the Serine 155 of murine BAD is within the BH3 region of murine BAD, which comprises the amino acid positions 151 to 159 of murine BAD or SEQ ID NO:2 (specification, page 13, last paragraph). In addition, it is noted that it is well known in the art that the BH3 region of BAD is necessary for binding and forming heterodimer with Bcl-2 molecules, and that a conformational change possibly take place in either Bcl-2 or the BH3 peptide upon binding (Letai, A et al, 2002, Cancer Cell, 2: 183-192, especially page 188, first column).

One cannot extrapolate the teaching of the specification to the scope of the claims because of the following reasons: It is unpredictable that substitution of Serine 118 of SEQ ID NO:1 with any amino acid, which is not a conservative substitution, would result in a mutant of BAD that has cell death promoting activity as claimed. As disclosed in the specification, when Serine 155 of murine BAD is replaced with Aspartic

acid (S155D), there is no pro-apoptotic activity of the S155D mutated BAD as compared to wild type BAD (p.89, second paragraph, and figure 12C). Further, since BH3 region of BAD is necessary for binding and forming heterodimer with Bcl-2 (Letai, A et al, *supra*), and since Serine 155 is located at the center of the BH3 domain (as disclosed in the specification, *supra*), one cannot predict that substitution of Serine 118 of SEQ ID NO:1 with any amino acid, which is not a conservative substitution, would not distort the conformation of the BH3 region and prevent binding or forming heterodimer with Bcl-2, which is necessary for cell death promoting activity of BAD.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

2. Claims 1-3, 10, 13, 16, 19, 22, 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide or fragment thereof, wherein a) said polypeptide or fragment thereof is at least 95% homologous to SEQ ID NO:1, b) said polypeptide or fragment thereof has Alanine at a position corresponding to the position 118 of SEQ ID NO:1, said position being identified by aligment of the amino acid sequence of said polypeptide or fragment thereof to the BH3 domain of SEQ ID NO:1, and c) said polypeptide or fragment thereof has cell death promoting activity *"in vitro"*, does not reasonably provide enablement for a polypeptide or fragment thereof, wherein a) said polypeptide or fragment thereof is at least 95% homologous to SEQ ID NO:1, b) said polypeptide or fragment thereof does not have a Serine at a position corresponding to the position 118 of SEQ ID NO:1, said position being identified by aligment of the amino acid sequence of said polypeptide or

fragment thereof to the BH3 domain of SEQ ID NO:1, and c) said polypeptide or fragment thereof has cell death promoting activity "in vivo". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-3, 10, 13, 16,19, 22, 28 are drawn to a polypeptide or fragment thereof, comprising a mutant Bcl-X_L /Bcl-2 associated cell death regulator (BAD), wherein a) said polypeptide or fragment thereof is at least 95% homologous to SEQ ID NO:1, or identical to SEQ ID NO:1, except that the amino acid at position corresponding to position 118 of SEQ ID NO:1 is an amino acid other than Serine, b) said polypeptide or fragment thereof does not have a Serine at a position corresponding to the position 118 of SEQ ID NO:1, said position being identified by aligment of the amino acid sequence of said polypeptide or fragment thereof to the BH3 domain of SEQ ID NO:1, and c) said polypeptide or fragment thereof has cell death promoting activity. The amino acid at said position corresponding to position 118 of SEQ ID NO:1 is not Glycine, or Alanine.

Claims 1-3, 10, 13, 16,19, 22, 28 encompass a polypeptide or fragment thereof, comprising a mutant Bcl-X_L /Bcl-2 associated cell death regulator (BAD), wherein a) said polypeptide or fragment thereof is at least 95% homologous to SEQ ID NO:1, or identical to SEQ ID NO:1, except that the amino acid at position corresponding to position 118 of SEQ ID NO:1 is an amino acid other than Serine, b) said polypeptide or fragment thereof does not have a serine at a position corresponding to the position 118 of SEQ ID NO:1, said position being identified by aligment of the amino acid sequence of said polypeptide or fragment thereof to the BH3 domain of SEQ ID NO:1, and c) said

polypeptide or fragment thereof has cell death promoting activity "in vivo". The amino acid at said position corresponding to position 118 of SEQ ID NO:1 is not glycine, or alanine.

The specification discloses that substitution of Serine 155 with Alanine (BAD S155A) in murine BAD (SEQ ID NO2) promotes cell death of Hela cells transfected with BAD or BAD mutants (Example 8 on page 86 bridging page 87). No disclosure is found in the specification concerning promoting of cell death *in vivo* by the mutated BAD S155A).

One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between cell death promoting activity of the mutated BAD S155A in transformed Hela cells with cell death promoting activity of the mutated BAD S155A *in vivo*. Charateristics of transformed Hela cells are different from target cells *in vivo*, and the *in vitro* conditions are different from *in vivo* conditions. In transformed Hela cells, the mutated BAD is artificially overepxressed, wherein the increase in the concentration of BAD could effect its competition with BAX for binding to Bcl-X_L and promote cell death activity (specification, page 3, second paragraph). Further, characteristics of cultured cell lines generally differ significantly from the characteristics of cells *in vivo*. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even

for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract).. The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may

not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that,

petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary - type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, the mutated BAD would promote cell death activity.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

REJECTION UNDER 35 USC 102

Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by US 5,965703.

Claim 25 is drawn to a mutated isolated or synthetic polypeptide of BAD of claim 1, or fragment thereof, wherein said polypeptide or fragment thereof comprises the amino acid sequence corresponding to positions 103-123 of SEQ ID NO:1.

Due to the indefinite language of claim 25, it is assumed for the purpose of compact prosecution that claim 25 is drawn to an isolated or synthetic polypeptide BAD, or fragment thereof, wherein said polypeptide or fragment thereof comprises the amino acid sequence corresponding to positions 103-123 of SEQ ID NO:1.

It is noted that the amino acid sequence corresponding to positions 103-123 of SEQ ID NO:1 is a fragment of the wild type human BAD, having Serine at position 118 (see Sequence listing, SEQ ID NO:1).

US 5,965703 teaches a human BAD sequence, SEQ ID NO:2, which is 100% identical to the full length of the claimed SEQ ID NO:1, from amino acids 1 to 168, as shown by MPSRCH sequence similarity search (MPSRCH search report, 2001, 09-580523-1b.rai, pages 1-2).

Thus the sequence taught by US 5,965703 seems to be the same as the claimed sequence.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

January 9, 2003